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Impact of bipolar disorder on eating disorders severity in real-life settings

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ABSTRACT

Background: Comorbidity of bipolar disorder (BD) and eating disorders (ED) is common and increases the course and severity of BD. However, the impact of comorbid BD on the clinical profile of ED patients remains unclear. Most studies have focused on patients primarily assessed for BD and data on patients with a primary diagnosis of ED are sparse. We investigated the association between a dual diagnosis and severity in terms of clinical, neuropsychological dimensions and daily functioning.

Method: Two hundred and sixty-one patients with ED were consecutively recruited. BD was screened with the MINI and further confirmed in the French expert centre network. The severity of ED symptoms was assessed with the EDE-Q and EDI-2, daily functioning with the FAST. The neurocognitive assessment targeted attention, set-shifting and decision-making.

Results: Forty-nine patients screened positive for BD, but diagnosis was confirmed in only thirty patients (11.5% of the cohort). After multiple adjustments, comorbidity was associated with greater severity on the total score and three subscales of the EDE-Q and on four of the ten dimensions of the EDI-2. Comorbid BD was associated with lower daily functioning but not with lower neuropsychological performance.

Limitations: Sample referred to specialist clinics not large enough to authorize an analysis by subtype and cross-sectional evaluation.

Conclusion: The association between ED and BD increases ED severity for most of these core features. It negatively impacts daily functioning. The results also highlight issues about the validity of screening tools to detect BD in patients with ED.

1. Introduction

The lifetime prevalence of eating disorders (ED) in adults is about 0.6% for anorexia nervosa (AN), 1% for bulimia nervosa (BN), and 3% for binge eating disorder (BED) (Treasure et al., 2010). These disorders are often chronic, relapsing, and devastating. The lifetime prevalence of bipolar 1 (BD-I) disorder is 0.6%, bipolar 2 (BD-II) 0.4%, subthreshold BD 1.4%, and bipolar spectrum 2.4% (Merikangas et al., 2011). The frequent comorbidity between these disorders has been noted in reviews since the 90s (Mury et al., 1995). The prevalence is variable, depending on the recruited population profile and the tools and diagnostic classification, but it is consistently very high. For example, several systematic literature reviews have reported that between 5.3% and 31% of patients with BD suffer from an ED, while approximately 8% of patients with ED have BD during their lifetime (Álvarez Ruiz and

Gutiérrez-Rojas, 2015; Godart et al., 2008; McElroy et al., 2006, 2005). The comorbidity of EDs and BD is increasingly studied for several reasons: treating one disorder could worsen the other and comorbidity could worsen the prognosis of both disorders, thereby increasing the rate of suicide attempts. Based on subtypes, BD seems to be more associated with ED with binge eating episodes (BN, BED, AN purging) (McElroy et al., 2016b; Thiebaut et al., 2018), but the data are more variable regarding the preferential association between ED and BD type 1 or type 2.

Several studies conducted in samples primarily assessed for BD have found that this comorbidity worsens BD, with more depressive episodes, lower functioning, an earlier age of the BD onset, and higher degrees of suicidality, anxiety disorder comorbidity, and mood instability, particularly depressive episodes (Brietzke et al., 2011; McElroy et al., 2016b). BD seems to be more frequently associated with

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ED with binge eating episodes (McElroy et al., 2016b; Thiebaut et al., 2018), with the clinical implication being more addiction and more impulsivity (Jen et al., 2013). In contrast, few studies have assessed the impact of this comorbidity on ED and their course. One study suggested that this comorbidity increases mortality in ED patients (Kask et al., 2016). To our knowledge, no study has yet assessed the impact of comorbid BD on the severity and course of ED in a sample of patients primarily assessed for ED.

Therefore, this study assessed the association between comorbid BD and ED severity in patients primarily seen for an ED. We hypothesized that comorbid BD would be associated with more severe ED on both clinical and neuropsychological dimensions, with lower daily functioning.

2. Methods

2.1. Participants

Overall, 296 outpatients with EDs as defined by the DSM-5 were consecutively assessed in an eating disorders unit in Montpellier, France, between February 2012 and October 2014. Patients with EDs (or suspected EDs) are sent on to this second-line unit (e.g. on caregiver's referral) for multidisciplinary assessment, diagnostic confirmation, and organisation of care. This ancillary study to a larger prospective project was approved by the local ethics committee (CPP Sud Méditerranée IV) and signed informed consent was obtained from all participants (and from parents for underage participants). Research was conducted according to the tenets of the Declaration of Helsinki. Inclusion criteria were as follows: 15 years or older, French speaking, and DSM-5-based diagnosis of ED. Exclusion criteria were as follows: presenting with a physical condition that precluded study participation ($n = 15$) and refusal to participate in the study ($n = 20$). Thus, 261 participants were finally included in the analysis (AN = 139, BN = 67, BED = 30, and other ED ($n = 25$)). Given their clinical heterogeneity, we grouped under the term "other ED" all patients with "Other Specified Feeding or Eating Disorder" or "unspecified Feeding or Eating Disorder".

2.2. Clinical assessment

The multidisciplinary clinical assessment was carried out by experienced psychiatrists, psychologists and nutritionists. The diagnosis of ED was established by consensus using the best-estimated procedure through medical records and information from relatives, the non-structured clinical assessments of psychiatrists and nutritionists, and a structured evaluation with the Mini-International Neuropsychiatric Interview (MINI, Version 5.0.0). All investigators were beforehand trained to use the MINI. The diagnosis of BD was first indicated by the MINI in all patients (including those with known BD). These patients were then referred to the French expert centre network for confirmation of the diagnosis (with exception of patients with a known BD already monitored in this expert centre. The same package of evaluations has been adopted by all centres of the network and the full assessment is performed by members of a specialized multidisciplinary team. Patients with BD who consent to participate in the assessment protocol (and who were not currently in a full BD episode) are then invited to complete the assessment procedure over a period of about 2 days (see Henry et al., 2011 for a complete description of the procedure used for mood assessment).

In addition, patients completed questionnaires that assessed key features of EDs:

- The EDE-Q (Luce and Crowther, 1999) is a 33-item screening tool to evaluate ED symptoms. It measures disordered eating over a 28-day period and is scored across four subscales that explore the four core clinical dimensions of ED: eating concern, body shape concern,

weight concern, and restraint.

- The EDI-2 (Garner, 1991) is a self-report measure of disordered eating attitudes and behaviours and the personality traits common to individuals with ED. Eleven subscales (drive for thinness, bulimia, body dissatisfaction, ineffectiveness, perfectionism, interpersonal distrust, interoceptive awareness, maturity fears, asceticism, impulse regulation, social insecurity) evaluate the symptoms and psychological correlates of EDs.
- The Functioning Assessment Short Test (FAST) (Moser et al., 2013; Rosa et al., 2007) is an interview-administered instrument designed to evaluate functioning across multiple domains in patients with psychiatric disorders. It comprises 24 items divided among six areas of functioning: autonomy, occupational functioning, cognitive functioning, financial issues, interpersonal relationships and leisure time. The higher the score, the more severe the difficulties are. This scale was used only for the subsample of patients over 18 years old.

Patients also underwent neuropsychological evaluation. This assessment targeted the neurocognitive dimensions reported to be impaired in ED (Guillaume et al., 2015; Roberts et al., 2007):

- The d2 test (Brickenkamp, 1962), which measures processing speed, rule compliance, and quality of performance, providing a neuropsychological estimation of individual attention and concentration performance. Originally developed to measure driving aptitude and efficiency, the d2 test has become the mainstay of attentional assessment in Europe.
- The Iowa gambling task (IGT) (Bechara et al., 1994), which is designed to measure decision-making under conditions of uncertainty. The task emphasizes the learning of reward and punishment combinations. Choices are classified as advantageous or disadvantageous. The IGT net score was calculated as the difference between the number of advantageous and disadvantageous choices, with higher scores indicating better performance.
- The Brixton test (Burgess, 1997), is a computer-administered test that presents the examinee with ten numbered circles, with one filled in blue. The blue circle moves around according to various patterns that change after a set is completed. Participants identify where the blue circle will move next and must reason through the pattern. The test consists of 56 trials with 8 rule changes. Set shifting difficulty is measured by the number of times a participant incorrectly predicts where the circle will move.

2.3. Statistical analysis

Associations between BD diagnosis and patient characteristics were quantified with odds ratios (ORs) and their 95% confidence intervals (CI). The sociodemographic and clinical variables associated with BD (at $p < 0.10$) were included in logistic regression models to estimate the adjusted ORs for ED indexes and functional measurements. The significance level was set at $p < 0.05$. Analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC, USA).

3. Results

According to the evaluations in the ED unit, 49 cases of BD were diagnosed with the MINI. The diagnosis was confirmed for 30 of these patients after a broader and more comprehensive assessment in the French expert center network, thus indicating that 11.5% of the cohort had comorbid BD.

Overall, bipolar comorbidity affected 6.5% (9/139) of the patients with AN, 16.4% (11/67) of those with BN, 16.6% (5/30) of those with BED, and 20% (5/25) of those with other ED (Table 1).

Table 1
Distribution of bipolar subtypes according the subtype of eating disorder.

	Subtype of ED		BN		BED		Other ED		Overall ED	
	AN N = 139		N = 67		N = 30		N = 25		N = 261	
	n	%	n	%	n	%	n	%	n	%
No BD	130	93.52	56	83.58	25	83.33	20	80.00	231	88.50
BD	9	6.48	11	16.42	5	16.67	5	20.00	30	11.50
BD type 1	2	1.44	5	7.46	3	10.00	2	8.00	12	4.60
BD type 2	7	5.04	6	8.96	2	6.67	3	12.00	18	6.90

Table 2
Sociodemographic and clinical characteristics of patients according to bipolar disorder.

Variable	Bipolar disorder		Yes N = 30		OR [95% CI]	p-value
	No N = 231		n	%		
Age, in years ^a	24.92 (15.08–65.83)		26.38 (18.92–63.08)		1.02 [0.99;1.05]	0.28
Sex					–	NA
Male	11	4.76	0	0.00		
Female	220	95.24	30	100.00		
Type of bipolar disorder					–	NA
BD1			12	40.00		
BD2			18	60.00		
Age of BD onset, in years ^a			16.5 (8–31)			
Age of ED onset, in years ^a	17 (6–65)		18 (11–51)		1.01 [0.97;1.05]	0.58
History of hospitalization for ED						
No	143	62.17	12	40.00	1	0.02
Yes	87	37.83	18	60.00	2.47 [1.13;5.37]	
Vomiting or laxatives or diuretics						
No	111	48.05	10	33.33	1	0.13
Yes	120	51.95	20	66.67	1.85 [0.83;4.12]	
Major depressive episode (past or actual)						NA
No	74	32.46	0	0.00		
Yes	154	67.54	30	100.00		
Anxiety disorders						
No	114	49.57	6	20.00	1	0.004
Yes	116	50.43	24	80.00	3.93 [1.55;9.97]	
Tobacco						
No	139	61.23	12	40.00	1	0.03
Yes	88	38.77	18	60.00	2.37 [1.09;5.16]	
Substance use disorders (other than tobacco) ^b						
No	218	94.37	23	76.67	1	0.002
Yes	13	5.63	7	23.33	5.10 [1.85;14.1]	
Lifetime history of suicide attempts						
No	180	77.92	16	53.33	1	0.005
Yes	51	22.08	14	46.67	3.09 [1.41;6.75]	
Lifetime history of violent suicide attempts						
No	43	89.58	9	81.82	1	0.48
Yes	5	10.42	2	18.18	1.91 [0.32;11.4]	

NA: test non-applicable.

^a Variables are expressed as median [minimum value-maximum value].

^b Alcohol $n = 7$, cannabis $n = 7$, cannabis and cocaine = 2, cannabis and alcohol $n = 2$, cocaine $n = 1$, benzodiazepine $n = 1$.

3.1. Association between comorbid BD and psychiatric comorbidity

Patients with a diagnosis of BD reported more anxiety disorders (defined as either obsessive-compulsive disorder, generalized anxiety disorder, panic disorder or post-traumatic stress disorder) and substance use disorders, were more often smokers, and had a higher lifetime history of suicide attempts ($p < 0.05$ for all these comparisons) (Table 2). Subsequent analyses were thus adjusted for these factors.

3.2. Association between comorbid BD and ED severity

Patients with a comorbid BD also had significantly higher EDE-Q total scores and subscale scores: eating concern, shape concern and weight concern in crude and adjusted association. Similarly, on the EDI-2 scale they had significantly higher scores on ten of the eleven assessed dimensions in crude and on four dimensions after adjustment: body dissatisfaction, perfectionism, interoceptive awareness, and impulse

regulation (Table 3).

3.3. Association between comorbid BD and neuropsychological performance

Non-adjusted associations between neuropsychological performance and comorbid BD are presented in Table 4. The comorbidity was not associated with a difference in neuropsychological performance on the IGT, d2 test or Brixton test.

3.4. Association between comorbid BD and daily functioning

In the subsample of patients older than 18 years, those with a diagnosis of BD had significantly more difficulties in functioning, with higher total scores on the FAST scale and its two dimensions: cognitive functioning and interpersonal relationships, even after adjustment for potential confounders (Table 5).

Table 3
Non-adjusted and adjusted associations between ED indices and comorbid bipolar disorders.

	Bipolar disorder		Model 1 OR [95% CI]	p-value	Model 2 OR [95% CI]	p-value
	NoN = 231 median (min-max)	YesN = 30 median (min-max)				
EDE-Q total score	3.69 (0.14–6)	4.65 (0.94–5.64)	1.87 [1.31;2.67]	0.0006	1.55 [1.08;2.22]	0.02
EDE-Q subscales						
- Restraint	2.8 (0–6)	4.5 (0–6)	1.30 [1.05;1.60]	0.02	1.12 [0.89;1.41]	0.33
- Eating concern	3 (0–6)	4 (0.8–6)	1.56 [1.19;2.04]	0.001	1.42 [1.05;1.91]	0.02
- Weight concern	4 (0–6)	5 (0.6–6)	1.59 [1.18;2.12]	0.002	1.41 [1.04;1.91]	0.03
- Shape concern	4.5 (0–6)	5.63 (2.38–6)	1.99 [1.34;2.94]	0.0006	1.72 [1.16;2.54]	0.007
EDI-2 subscales						
- Drive for thinness	13 (0–21)	16 (0–20)	1.08 [1.01;1.16]	0.03	1.04 [0.96;1.12]	0.34
- Bulimia	3 (0–21)	9 (0–18)	1.06 [1.01;1.13]	0.03	1.04 [0.98;1.10]	0.23
- Body dissatisfaction	12 (0–24)	20 (7–27)	1.09 [1.03;1.15]	0.004	1.07 [1.00;1.14]	0.04
- Ineffectiveness	9 (0–30)	14 (0–28)	1.08 [1.03;1.13]	0.003	1.05 [0.99;1.11]	0.08
- Perfectionism	7 (0–18)	9.5 (0–18)	1.15 [1.05;1.26]	0.002	1.11 [1.01;1.22]	0.04
- Interpersonal distrust	5 (0–18)	9 (0–15)	1.12 [1.03;1.21]	0.009	1.07 [0.97;1.17]	0.18
- Interoceptive awareness	8 (0–30)	17.5 (0–30)	1.11 [1.05;1.17]	0.0001	1.08 [1.01;1.14]	0.02
- Maturity fears	4 (0–24)	8 (0–23)	1.04 [0.98;1.11]	0.20	1.04 [0.97;1.11]	0.27
- Asceticism	7 (0–21)	10 (2–19)	1.13 [1.04;1.22]	0.004	1.08 [0.99;1.19]	0.09
- Impulse regulation	4 (0–25)	10.5 (0–29)	1.12 [1.06;1.18]	<0.0001	1.09 [1.03;1.15]	0.003
- Social insecurity	7 (0–21)	10.5 (1–17)	1.10 [1.02;1.19]	0.02	1.06 [0.97;1.16]	0.19

Model 1: crude association.

Model 2: adjustment for anxiety disorders, substance use disorder, tobacco and suicide attempts.

Table 4
Non-adjusted associations between neuropsychological performance and comorbid bipolar disorder.

Bipolar disorder	No. N = 231 median (min-max)	YesN = 30 median (min-max)	OR [95% CI]	p-value
d2 test: total number of items processed	472 (162; 985)	470 (304; 575)	1.00 [0.99;1.00]	0.54
d2 test: total number of errors	15 (0; 136)	12 (0; 108)	1.00 [0.98;1.02]	0.99
d2 test: percentage of errors	3.32 (0; 33.95)	2.34 (0; 21.82)	0.99 [0.91;1.08]	0.82
IGT (net score)	4 (-56; 80)	6 (-50; 62)	1.01 [0.99;1.03]	0.54
Brixton test	7 (1; 10)	7 (2; 10)	0.94 [0.78;1.14]	0.55

4. Discussion

In this large, well-defined and consecutively recruited sample of patients suffering from ED, we found that, after adjustment for anxiety disorders, substance use disorder, tobacco and suicide attempts, comorbid BD was associated with more severe ED on most of the core dimensions (body dissatisfaction, shape concern, weight concern, eating concern, impulse regulation, interoceptive awareness and perfectionism). It was also associated with lower daily functioning and more frequent psychiatric disorders. Reciprocally, previous results, in clinical samples of patients primarily referred for BD, suggest that comorbidity increases the severity of BD (McElroy et al., 2011, 2016a). This study also sustains previous data suggesting that comorbid BD is

more prevalent in BN and BED than in AN. Last, although no data has thus far been available on this topic, our results suggest no additive effect of comorbid BD on the putative neuropsychological impairment in ED.

These results suggest that patients with BD should be assessed for EDs and patients with ED should be assessed for BD to ensure comprehensive prognosis and an optimal treatment program.

We found considerable inconsistency between the rate of BD using a validated screening tool (the MINI) and that resulting from more in-depth assessment. The validity of the MINI as screening tool for the BD has been a topic of discussion. The inter-rater and test-retest reliability for the MINI has previously been found satisfactory (Lecrubier et al., 1997). Nevertheless, the diagnosis was much more frequently

Table 5
Non-adjusted and adjusted associations between functioning measurements and comorbid bipolar disorder (for patients above 18 years only).

	Bipolar disorder		Model 1 OR [95% CI]	p-value	Model 2 OR [95% CI]	p-value
	No N = 202 n; median (min-max)	Yes N = 30 n; median (min-max)				
FAST total score	143; 19 (0; 61)	24; 33 (7; 52)	1.04 [1.01;1.08]	0.005	1.03 [1.00;1.07]	0.05
FAST subscales						
- Autonomy	191; 3 (0; 11)	28; 5 (0; 11)	1.16 [1.02;1.33]	0.03	1.14 [0.99;1.32]	0.06
- Occupational functioning	156; 3 (0; 15)	24; 5.5 (0; 15)	1.05 [0.96;1.16]	0.28	1.04 [0.94;1.15]	0.41
- Cognitive functioning	189; 4 (0; 15)	28; 6.5 (0; 14)	1.17 [1.05;1.30]	0.004	1.15 [1.02;1.29]	0.02
- Finances	193; 1 (0; 6)	28; 3 (0; 6)	1.27 [1.06;1.52]	0.01	1.15 [0.94;1.40]	0.17
- Interpersonal relationships	178; 7 (0; 18)	28; 10 (0; 17)	1.16 [1.05;1.27]	0.002	1.11 [1.01;1.23]	0.03
- Leisure time	191; 2 (0; 6)	28; 3.5 (0; 6)	1.27 [1.03;1.56]	0.03	1.19 [0.96;1.48]	0.12

Model 1: crude association.

Model 2: adjustment for anxiety disorders, substance use disorder, tobacco and suicide attempts.

ascertained when using the MINI. Verhoeven et al. (2017) found that the proportion of mood disorders was 1.65 times higher when measured with the MINI than when diagnosed by the clinician. Presence of manic episodes according to the MINI were also shown to have poor positive predictive in their seminal paper (Lecrubier et al., 1997).

This highlights the issue of using diagnostic tools to detect BD in samples of patients with ED. In a recent review on the prevalence of ED associated with BD, it emerged that studies with diagnostic accuracy were unfortunately quite rare and that the tools used for diagnosis in large part explained the difference in prevalence from one study to another (Thiebaut et al., 2018). Two helpful tools in BD diagnosis are the mood disorder questionnaire (MDQ) and the Composite International Diagnostic Interview 3 (CIDI 3.0). Caution is nevertheless needed because Zimmerman et al. (2011) found that patients who screened positive were significantly more likely to have a current and lifetime diagnosis of a specific phobia, post-traumatic stress disorder, alcohol and drug use disorders, any eating disorder, any impulse control disorder, or attention deficit disorder. There may be a slight tendency toward over-diagnosis using the MDQ, but this is the only tool that has been used in ED patients. Among patients being evaluated for EDs, the MDQ shows promise as a screening questionnaire for BD (Nagata et al., 2013).

The chronology of onset of BD and ED appeared to be relatively homogeneous, with 11 patients (39%) developing an ED after BD, 11 patients (39%) developing an ED before BD and 6 patients (21%) at the same time. This is consistent with the literature. For example, Godart et al. (2015) found onset of BD occurring around the same time as or later than ED onset. Conversely, other studies (McElroy et al., 2011; Ramacciotti et al., 2005) found BD onset occurring before the ED onset among patients with a mean age of 40–41 years.

It is well known that EDs are associated with serious suicide attempts (AN patients are more likely to have made a serious attempt) (Guillaume et al., 2011), and we found that bipolar comorbidity increased the risk of suicide attempts but not the risk of violent attempts. This may be due to the heightened impulsivity with this comorbidity. BD is characterized by impaired decision-making captured in impulsivity and risk-taking (Mason et al., 2014), and impulsive attempts are known to be less severe (Lim et al., 2016). However, in this sample comorbid BD was not associated with poorer decision-making.

Studies have found more severe neuropsychological impairments in patients with BD and a comorbid substance use disorder or comorbid suicidal behaviour disorder (Balanzá-Martínez et al., 2015; Richard-Devantoy et al., 2016). Contrary to our expectations, the comorbid BD in the population of ED patients did not lead to impaired neuropsychological performance. An explanation could be related to the neuropsychological assessment carried out in our study, which was very focused on executive function impaired in ED. It might be hypothesised that these targeted functions are not the ones potentially impacted by a dual diagnosis. Most studies found that BD patients with a history of comorbid of substance use disorders show more severe impairments, especially in verbal memory (Balanzá-Martínez et al., 2015). The fact that we found a significant difference in cognitive functioning according to the FAST scale goes in this direction. Indeed, the cognitive functioning subscore of the FAST is related to the ability to solve problems, perform simple mental calculations, learn new information and remember learned information (Rosa et al., 2007). Future studies should include a more comprehensive assessment of executive functions to test this hypothesis.

These results confirm that EDs with binge eating episodes or compensatory behaviours could be associated with more comorbid BD. Findings indicate that emotional dysregulation is associated with ED symptoms in BN and BED (Gianini et al., 2013; Lavender et al., 2014). Individuals with BD also display emotional dysregulation and have greater overall difficulty regulating emotions compared with healthy controls (Bayes et al., 2016). Higher levels of emotional reactivity were observed in BD with compared to BD without binge eating behaviour

(Boulanger et al., 2018). This might be due to the increased impulsivity or with a more severe degree of emotional dysregulation.

Our study has some notable strengths. To our knowledge, it is the first to focus on the impact of comorbid BD on the severity and course of EDs in a sample of patients primarily assessed for ED. The sample was consecutively recruited and was large enough to allow us to control for the impact of covariables, like psychiatric comorbidities. We used a large set of validated tools to assess the ED characteristics in depth, including neuropsychological and functional features. Furthermore, the diagnosis of BD was validated by specialists of this disorder in the French expert centre network. Screening for BD with the MINI yielded 47 patients with a suspicion of diagnosis, but only 64% had this diagnosis confirmed.

The current findings must nevertheless be interpreted in light of the study limitations. First, despite the overall size of the sample, it was not sufficient to authorize an analysis by subtype (both ED and BD subtypes), although we suspect that examining the potential interactions between the ED subtypes and BD would be a useful future direction as well as an adjustment on the age of the patients and on the duration of the disorders. Also, regarding BD diagnosis, although our methodology ensured the absence of false positives, we cannot exclude the possibility of false negatives. Last, we studied only those patients who had been admitted to our second-line unit, which explains the high rates of patients with AN and those with previous hospitalizations. Hence, our results can be generalized essentially to patients admitted to a specialized unit.

In conclusion, the association between BD and EDs appears to be frequent and we suggest that comorbid BD is associated not only with an aggravation of the ED symptoms and lower daily functioning, but also with more anxiety disorders, substance use disorders and tobacco consumption, as well as a history of suicide attempts. This comorbidity thus needs to be assessed in all patients with ED.

Conflict of interest

S Guillaume reported that he received funding as a consultant by Janssen, Otsuka and Lundbeck Companies. Other authors report no financial relationships with commercial interests related to this study.

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Conflict of interest

S Guillaume reported that he received funding as a consultant by Janssen, Otsuka and Lundbeck Companies. Other authors report no

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